COVID-19 ACUTE MYOCARDIAL INJURY

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RETROSPECTIVE CLINICAL TRIALS

• COVID-19 primarily effects the upper respiratory tract causing pneumonia, respiratory failure and acute respiratory distress syndrome, there have also been many reports of cardiovascular involvement

• Retrospective Single Study Trials
  • Huang et al. Lancet 2020
  • Chen et al. Lancet 2020
  • Wang et al. JAMA 2020

• Retrospective Multi Center Studies
  • Wu et al. JAMA 2020
  • Guan et al. NEJM 2020

• COVID-19 infection can also present with isolated cardiac symptoms, even in the absence of respiratory symptoms (Inciardi et al. JAMA Cardiol 2020)
Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19)

Riccardo M. Inciardi, MD; Laura Lupi, MD; Gregorio Zaccone, MD; Leonardo Italia, MD; Michela Raffo, MD; Daniela Tomasoni, MD; Dario S. Cani, MD; Manuel Cerini, MD; Davide Farina, MD; Emanuele Gavazzi, MD; Roberto Maroldi, MD; Marianna Adamo, MD; Enrico Ammirati, MD; Gianfranco Sinagra, MD; Carlo M. Lombardi, MD; Marco Metra, MD

• 53F with no prior medical history presenting to Niguarda Hospital in Milan, Italy in March 2020 with chest pain and dyspnea
• Presenting VS: afebrile, HR 100 bpm, BP 90/50 mmHg, SpO2 98% RA
Table. Clinical Laboratory Results

<table>
<thead>
<tr>
<th>Measure</th>
<th>Reference range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>Blood cell count, ×10^12/μL</td>
<td>4.0-5.2</td>
<td>5.5</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.0-16.0</td>
<td>17.1</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>37.0-47.0</td>
<td>49.3</td>
</tr>
<tr>
<td>White blood cell count, per μL</td>
<td>4000-10 800</td>
<td>8900</td>
</tr>
<tr>
<td>Lymphocyte count, per μL</td>
<td>20.0-40.0</td>
<td>10.6</td>
</tr>
<tr>
<td>Platelet count, ×10^3/μL</td>
<td>130-400</td>
<td>152</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>136-145</td>
<td>129b</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>3.4-4.5</td>
<td>5.7a</td>
</tr>
<tr>
<td>Chloride, mEq/L</td>
<td>98-107</td>
<td>89b</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>8.60-10.20</td>
<td>8.63</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.60-1.00</td>
<td>0.75</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>0.5</td>
<td>1.3a</td>
</tr>
<tr>
<td>Creatine kinase-MB, ng/mL</td>
<td>&lt;4.9</td>
<td>20.3</td>
</tr>
<tr>
<td>High-sensitivity troponin T, ng/mL</td>
<td>&lt;0.01</td>
<td>0.24</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>&lt;300</td>
<td>5647</td>
</tr>
</tbody>
</table>

A. Electrocardiography showing sinus rhythm with low voltage in the limb leads, diffuse ST-segment elevation (especially in the inferior and lateral leads), and ST-segment depression with T-wave inversion in leads VI and aVR. B. Posteroanterior chest radiography at presentation. No thoracic abnormalities were noted.
• Retrospective studies from Wuhan University examining cardiovascular disease in COVID-19 (Guo et al. JAMA Cardiol 2020, Shi et al. JAMA Cardiol 2020)

• Patients with baseline cardiovascular disease have increased mortality during COVID-19
  • 7.62% mortality in patients without prior CVD and with normal TnT
  • 13.33% morality in patients WITH prior CVD and with normal TnT

• Patients who experience acute myocardial injury during COVID-19 infection have worse mortality even in the absence of baseline symptoms (although baseline cardiovascular disease + acute myocardial injury had higher mortality)
  • 37.5% mortality in patients without prior CVD with ELEVATED TnT
  • 69.44% mortality in patients WITH prior CVD and with ELEVATED TnT

• Acute myocardial injury alone, even without LV dysfunction, was associated with higher mortality, however those with LV dysfunction had the worst mortality of any age group

• Cardiovascular complications of COVID-19 infection are a major contributor to patient mortality, but the pathophysiology underlying this cardiac injury is not presently understood
PROPOSED MECHANISMS OF MYOCARDIAL INJURY

- Type I MI/Plaque Rupture
  - Increased rates of type I MI in influenza (Nguyen JAMA Cardiol 2016, Kwong NEJM 2018)

- Type II MI/Demand Ischemia
  - Similar to that seen in severe sepsis

- Acute Fulminant Myocarditis
  - Similar to that seen with MERS (Alhogbani Ann Saudi Med 2016)
  - Would require viremia and direct infection of myocardium since viral entry is most likely mediated by infection of nasopharyngeal cells, and virus was detected in blood in only a minority of patients (To Lancet Infect Dis 2020)

- Cytokine Storm-mediated Injury
  - Autoimmune response to viral infection mediates end-organ damage
  - “Secondary hemophagocytic lymphohistiocytosis”

  - Direct infection of cardiomyocytes
  - Vascular/Endothelial dysfunction

- Limited myocardial tissue pathology has been completed to date

Bonow, Fonarow, O’Gara, Yancy. JAMA Cardiology 2020
Pathological findings of COVID-19 associated with acute respiratory distress syndrome

Zhe Xu*, Lei Shi*, Yijin Wang*, Jiyuan Zhang, Lei Huang, Chao Zhang, Shuhong Liu, Peng Zhao, Hongxia Liu, Li Zhu, Yanhong Tai, Changqing Bai, Tingting Gao, Jinwen Song, Peng Xiao, Jinghui Dong, Jingmin Zhao, Fu-Sheng Wang

- 50 M with history of travel to Wuhan, China January 8-12, admitted to the Fifth Medical Center of PLA General Hospital in Beijing on Jan 21, 2020 with fevers. Unclear PMH

The pathological features of COVID-19 greatly resemble those seen in SARS and Middle Eastern Respiratory Syndrome (MERS) coronaviruses. SARS-CoV-2 infection in this patient might help physicians to formulate a timely therapeutic strategy for similar severe patients and reduce mortality.

Although corticosteroid treatment is not routinely used in COVID-19, we treated the patient with intravenous methylprednisolone (500 mg twice daily, orally) as antiviral therapy, and received supplemental oxygen through a face mask. He was immediately given invasive ventilation, chest compressions, and adrenaline injection. Unfortunately, the patient had sudden cardiac arrest. He was given interferon alfa-2b (5 million units twice daily, intravenously) to prevent cytokine storm and multi-organ injury in this patient.

Additional treatment was given: meropenem (0.4 g once daily, intravenously) to prevent drug-induced liver injury as the cause. There were no conclusive evidence to support SARS-CoV-2 infection as the cause. There were no obvious intranuclear or intracytoplasmic viral inclusions suggesting that SARS-CoV-2 infection might not directly cause the disease severity and mortality.

Our clinical and pathological findings in this severe case of COVID-19 can not only help to identify a cause for some diseases, but also provide guidance on clinical and biological strategies against COVID-19 and improve clinical strategies against other substantial damage in the heart tissue (figure 2D).

Peripheral blood was prepared for flow cytometric analysis of peripheral blood leukocytes, which 31.6% cells were perforin positive, 64.2% cells were granulysin positive, and 45.2% cells were positive for both. CD8 T cells were found to be CD8 T cell populations that harbours high concentrations of cytotoxic granules, in particular perforin and granzyme B, suggesting that SARS-CoV-2 infection might not directly cause the disease severity and mortality. In addition, the liver biopsy specimens of the patient with COVID-19 showed moderate microvesicular steatosis and mild lobular activity, but there was no evidence of hepatitis or drug-induced liver injury as the cause. There were no obvious intranuclear or intracytoplasmic viral inclusions in the liver tissue, suggesting that SARS-CoV-2 infection might not directly cause the disease severity and mortality.

CD8 T cells, accounts for, in part, the severe immune injury in this patient. Our findings suggest that SARS-CoV-2 infection might be a critical factor associated with the disease severity and mortality.
• 69M presents to ED in Lombardy, Italy with cough, shortness of breath and weakness x 4 days
• CT Thorax with bilateral interstitial infiltrates, labs with leukocytosis and elevated inflammatory markers, ABG with pH 7.2
• TTE with LVEF 35% → 25% within 3 hours
• Cath unremarkable → IABP → worsening hypotension → VA-ECMO + intubation
• Transfer to tertiary MC → EMB performed

Myocardial localization of coronavirus in COVID-19 cardiogenic shock

Guido Tavazzi1,2, Carlo Pellegrini1,2, Marco Maurelli3, Mirko Belliato1, Fabio Sciutti1, Andrea Bottazzi1, Paola Alessandra Sepe1, Tulia Resasco5, Rita Camporotondo6, Raffaele Bruno1,2, Fausto Baldanz1,2, Stefania Paolucci4, Stefano Pelleghi1, Giorgio Antonio Iotti1,2, Francesco Mojoli1,2, Andrea Bottazzi5, Mirko Belliato1, Fabio Sciutti1, and Eloisa Arbustini6


Figure 1 Light microscopy immunostaining of the inflammatory infiltrate. (A,B) Low- and high-power views of endomyocardial biopsy, with sparse CD45RO positive interstitial cells. (C,D) Large, vacuolated macrophages immunostained with anti-CD68 antibodies. (E) Ultrastructural morphology of a large and cytopathic macrophage. (A–D: the bar scale is in the left low corner of each panel. E: the bar scale is in the right low corner of the panel and corresponds to 2 μm).

Figure 2 Examples of small groups of viral particles (A and B; panel C shows a higher magnification of one of the viral particles squared in dashed red box of panel B) or single particles (D–F) observed within the interstitial cells of the myocardium of the patient. The red arrows indicate the most typical and easy-to-recognize viral particles, whose size varies from about 70 nm to 120 nm (see the white bars in the panels). Morphology also shows small differences with more or less prominent spikes of the viral crown. The morphology may also show viral particle disruption (E, green arrow) or attenuation of spikes of the crown (D and F), or viral particles in budding attitude (F). (Bar scale: A and B, 200 nm; C, 50 nm; D, 100 nm; E, 100 nm; F, 50 nm).
The dominant process in all cases was consistent with diffuse alveolar damage, with a mild to moderate interstitial infiltrate of neutrophils that was restricted to the lungs. This process may involve activation of megakaryocytes, possibly to (but not surrounding) these individual necrotic myocytes. They did note some lymphocytes adjacent to (but not surrounding) these individual necrotic myocytes. Possibly early lymphocytic myocarditis

Bradley et al. Histopathological and Ultrastructural Findings in COVID-19 Infection
https://www.medrxiv.org/content/10.1101/2020.04.17.20058545v1
Post mortem analysis of 12 fatal cases presenting in Seattle, WA Feb-Mar 2020 (University of Washington)

Fox et al. Pulmonary and Cardiac Pathology in COVID-19: The First Autopsy Series from New Orleans
https://www.medrxiv.org/content/10.1101/2020.04.06.20050575v1.full.pdf
Post mortem analysis of 4 fatal cases at University Medical Center in New Orleans, LO (LSU/Tulane)
CONCLUSIONS

- Limited myocardial tissue pathology available
- Patient demographics from the autopsy series are limited
- No basic transcriptomic/molecular data available
- Limited cardiac functional data available